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Full Length Article

Role of FDG-PET scan in the management of pediatric mature B cell non-Hodgkin's lymphoma. CCHE experience

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KEYWORDS

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Abstract *Aim of work:* To evaluate the sensitivity (Se), specificity (Sp), and predictive values (PV) of PET scan during management of pediatric mature B cell non-Hodgkin's lymphoma (NHL) in comparison with conventional computed tomography (CT) scan.
Patients and methods: A retrospective study enrolled on pediatric NHL patients at Children Cancer Hospital Egypt (CCHE) during the period from July 2007 to the end of June 2013.
Results: For 115 pediatric patients diagnosed with mature B cell NHL, 152 PET and 152 CT scans were done simultaneously. Median age was 5.7 years. They were 85 males (74%) and 30 females (26%). One hundred twenty six scans (82.9%) were done for 100 (87%) Burkitt lymphoma (BL) patients, while 26 scans (17.1%) were done for 15 (13.0%) patients with diffuse large B cell NHL (DLBC). Nineteen examination (12.5%) were done before starting chemotherapy (group 1), 107 (70.3%) at time of evaluation (group 2), and 26 (17.1%) during follow up (group C). Overall sensitivity was 91.6% for PET and 70.0% for conventional CT ($p = 0.02$). Specificity was 84.1% for PET and 58.9% for CT ($p < 0.001$). Positive predictive value (PPV) for PET was 50%, while was 22% for CT scan ($p < 0.001$). Negative predictive value (NPV) for PET was 98%, and 92% for CT ($p = 0.01$).

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Conclusion: PET scan is significantly more sensitive than conventional CT in the management of aggressive pediatric mature B cell NHL. PET negativity is an excellent indicator of tumor response.

Introduction

Pediatric mature B-cell non-Hodgkin lymphomas (NHL) are highly aggressive malignant tumors. Over the past 25 years, multidisciplinary pediatric cooperative group collaborations have reported 99% overall survival rate in low risk patients, 90% in intermediate-risk, and a 70% to 80% in children with high risk [1–3].

Evaluation of residual masses in cases of incomplete remission is one of the major difficulties during treatment. Moreover, pathologic documentation may hold unnecessary risks [4–7].

18-F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) is a noninvasive, 3-dimensional imaging modality that has become widely used in the management of adults with malignant lymphomas. Current applications may include pretreatment staging, restaging, monitoring of therapy effect, and follow up (FU) [8–10]. However, only a few experiences have been reported in children with mature B cell NHL [11–13], with unsettled utility for response assessment [14–15].

The aim of the current study is to evaluate the sensitivity (Se), specificity (Sp), and predictive values (PV) of PET scan compared to conventional CT scan. In addition, we wanted to test the reliability of such a non invasive tool during management of pediatric mature B cell NHL, and its impact on the decision whether or not a biopsy should be taken.

Patients and methods

It is a retrospective study enrolled on newly diagnosed pediatric NHL patients treated at the Children Cancer Hospital Egypt (CCHE) during the period from July 2007 to the end of June 2013. Inclusion criteria were PET – in addition to conventional CT scan – done at any stage of the treatment. Blind revision of all PET and CT scans was specifically done for this study.

This study included 115 patients for whom 152 PET scan – in addition to conventional CT scan – was done at any stage of the treatment. All patients were treated and assessed according to the LMB 96 treatment protocol [16]. Staging was performed according to Murphy's classification [17]. Tumor resection and/or biopsy outside CCHE were not an exclusion criterion. Initial evaluation included clinical, and laboratory diagnostic workup. Written informed consent was obtained from each patient's parents. The local ethics committee approved this study. The end point used for final evaluation is the final clinical outcome at the end of the follow up period. Patients were followed up till 01/03/2014.

Conventional imaging

Tumor assessment was done using computed tomography (CT) with contrast (Sensation 16, Siemens; Light Speed VCT, GE Medical Systems). In cases with head and neck involvement or suspected meningeal infiltration, MRI was performed. All CT images were evaluated based on 1999 international workshop criteria (IWC) [5]. Radiological films were evaluated by two experienced pediatric radiologists blinded to the PET results specifically for the aim of the study. CT scan was used for initial evaluation, during treatment evaluation and follow up.

^{18}FDG-PET procedure

The use of standardized uptake values (SUVs) of the radiolabeled tracer 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) has a specific role in assessing patient response to therapy since increased accumulation of FDG relative to normal tissue is a useful marker [18]. Measuring methods of the rate of accumulation by [kBq/ml] reflects the relative tissue uptake of FDG. So the standardized uptake value (SUV) is commonly used as a relative measure of FDG uptake [19]. Whole-body ^{18}FDG-PET was acquired on a Discovery LS PET/CT imaging system (GE Medical Systems) 60–80 min after intravenous injection of 5–7 MBq/kg of ^{18}FDG or on a mCT Biograph imaging system (Siemens) after intravenous injection of 3 MBq/kg of ^{18}FDG. Children fasted at least 4 h before ^{18}FDG injection and blood glucose was controlled prior to the injection. Images were reconstructed by OSEM iterative reconstruction algorithm (ordered-subset expectation maximization) with and without attenuation correction. All ^{18}FDG-PET images were retrospectively reviewed on a dedicated workstation (Positoscope; Keosys, France). ^{18}FDG-PET was interpreted visually by at least two nuclear medicine physicians with expertise in lymphoma imaging using the five-point scale (Deauville criteria), as recently recommended by Lugano's recommendations in lymphoma [4].

^{18}FDG-PET analysis

In addition to the standard procedures, whole-body ^{18}FDG-PET was done for those patients. According to timing of the PET exam, patients were divided into 3 groups: *group 1:* PET done before starting chemotherapy, *group 2:* PET done to evaluate chemotherapy response according to treatment protocol (after 3 and 4 courses of chemotherapy for intermediate risk and high risk groups respectively), and *group 3:* PET done during follow up (FU) period (Fig. 1).

Statistical methods

The diagnostic performance of PET scan was estimated by calculating its sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) in relation to that of conventional radiology. Results were classified as true positive or negative, and false positive or negative supported by the status of the disease.

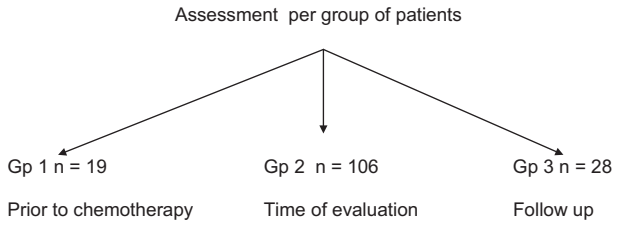

Figure 1 Patient grouping according to time of PET examination. Group 1: examination done prior to start of chemotherapy. Group 2: PET done at the time of evaluation according to the treatment protocol to assess tumor response to chemotherapy. Group 3: PET done after the end of chemotherapy as to document relapse.

Sample size calculation

Paired-sample specificity analysis

A sample size of 152 achieves 86% power to detect a difference of 0.27 between two diagnostic tests whose specificities are 0.85 and 0.58 [20]. This procedure uses a two-sided McNemar test with a significance level of 0.05000 [21]. The prevalence of disease in the population is 0.25. The proportion of discordant pairs is 0.32 [20,22–25].

Paired-sample sensitivity analysis

A sample size of 152 achieves 82% power to detect a difference of 0.26 between two diagnostic tests whose sensitivities are 0.89 and 0.63 [20]. This procedure uses a two-sided McNemar test with a significance level of 0.05 [21]. The prevalence of disease in the population is 0.25. The proportion of discordant pairs is 0.32 [20,22–25].

The lesions found on FDG-PET/CT and CT scans were compared. The concordance rate is defined as the number of lesions seen by both modalities divided by the number of lesions seen by at least one of the modalities. McNemar's test which is based on identifying the non-concordant lesions was used to compare the two modalities. All reported p values are based on this test.

Results

This study included 115 mature B cell NHL patients who underwent 152 scan during the period from 7/7/2007 to 31/12/2013. Median duration of follow up was 42 months, and ranged from 2 to 74 months.

Median age was 5.7 years (range 1–18 years). They were 85 males (74%) and 30 females (26%). One hundred Burkitt lymphoma patients (87%) underwent 126 PET scans (83.0%), while fifteen patients (13%) had diffuse large B cell (DLBL), and did 26 PET (17.0%).

In group 1; 19 PET scans (16.5%) were done before starting chemotherapy. Sixteen (84.2%) post surgical resection of intestinal mass (stage II disease), while the rest 3/19 (15.8%) as initial work up. For 8/19 (42%), PET confirmed the absence of residual disease, and patients were treated as low risk (LR). In 8/19 (42%), PET detected post operative residual tumor mass, and patients were upgraded to intermediate risk group.

In group 2; 107 PET (69.2%) were done at the time of re-evaluation of chemotherapy response. PET and CT were concordant in 67/107 (62.6%), and disconcordant in 40/107 (37.4%) of cases respectively. In disconcordant cases, PET was true negative in 35/40 cases (87.5%), false positive in 3/40 cases (7.5%), and true positive in 2/38 case (5%), with no false negative results.

In group 3, 26 PET (18.3%) were done during follow up. PET and CT were concordant in 20/26 (77%) of the cases, and disconcordant in 6/26 (23%). PET was true negative in 3/6 cases (50%), false positive in 2 cases (33%), true positive in one case (17%), and no false negative.

Overall, sensitivity was 89.4% for PET, and 63.1% for CT ($p = 0.02$). Specificity was 84.9% for PET, and 58.6% for CT ($p < 0.001$). PPV for PET was 45.9%, while was 17.9% for CT scan ($p < 0.001$). NPV for PET was 98.2%, while was 91.7% for CT ($p = 0.01$).

In BL, sensitivity was 91.6% for PET, and 66.6% for CT ($p = 0.08$). Specificity was 85.8% for PET, while was 58.4% for CT ($p < 0.001$). PPV and NPV were 40.7% and 98.9%, for PET, while were 14.5% and 94.2% for CT scan ($p < 0.001$, and 0.05 respectively).

In DLBC, sensitivity was 85.7% for PET while was 57.1% for CT ($p = 0.15$). Specificity was 80.0% for PET, while was 60.0% for CT ($p < 0.20$). PPV and NPV for PET were 60.0%, and 94.1% respectively, while were 33.3% and 80.0% for CT scan ($p < 0.07$, and 0.10) respectively (Table 1).

Discussion

This retrospective study was conducted in the Children Cancer Hospital Egypt. The main objective was to determine the role, and impact of ^{18}FDG-PET done during the course of chemotherapy and FU period on the physician decision to go for pathological documentation. Mature B cell NHL tends to relapse very early (within the first 6 months after end of treatment) [16]. The median duration of FU was 42 months (range 2–74 months). Our cutoff value was the patient final clinical outcome.

Assessment of response to chemotherapy with CT scans alone has its drawbacks. It lacks functional information and detection of lesions is poor contrast with the surrounding tissue [25]. As previously mentioned by many authors, the presence of residual mass by CT scan at time of evaluation during the course of chemotherapy poses many difficulties. Surgical or radiological documentation of viable tissue is sometimes difficult, invasive, and may pose unnecessary risks [4–7]. Functional imaging with PET scanning, explained by the superadded role of biological assessment through measuring the FDG uptake by the viable lymphomatous tissue, may help to resolve this dilemma [26]. Studies have proven its accuracy staging, restaging and as a prognostic indicator for the treatment outcome [27–30]. In the current study, PET done before stating chemotherapy excluded the presence of residual disease in 7% of the patients, and lead to their restratification as LR. They were all alive in CR by the end of the study. Meanwhile another 7% were upgraded to IR group as they had PET evidence of residual disease. The use of FDG-PET/CT resulted

Table 1 Sensitivity, specificity, PPV, NPV and confidence interval of the studied patients.

Results	All scans (n = 152)			BL (n = 126)			DLBC (n = 26)		
	PET	CT	p	PET	CT	p	PET	CT	p
Sensitivity	89.5% (75.7%-99%)	63.2% (41.5–84.8)	0.0253	91.7% (76–100)	66.7% (40–93.3)	0.083	85.7% (59.8–100)	57.1% (20.5–93.8)	0.157
Specificity	84.9% (78.9–91%)	58.6% (50.3–67)	< 0.001	85.8% (79.4–92.3)	58.4% (49.3–67.5)	< 0.001	80.0% (62.5–97.5)	60.0% (38.3–81.5)	0.205
PPV	45.9% (29.9–62%)	17.9% (8.7–27.1)	< 0.001	40.7% (22.2–59.3)	14.5% (5.2–23.9)	< 0.001	60.0% (29.6–90.4)	33.3% (6.7–60)	0.075
NPV	98.3% (95.9–99.9%)	91.7% (85.9–97.6)	0.011	98.9% (97–100%)	94.3% (88.8–99.7)	0.054	94.1% (82.9–100)	80.0% (59.8–100)	0.101

BL: Burkitt lymphoma, CI: confidence interval, DLBC: diffuse large B cell, NPV: negative predictive value, PPV: positive predictive value.

in upstaging 31% of patients with NHL in comparison to CT [31].

In group 2 and 3 patients (those who had PET at time of evaluation, or during FU), PET was very good negative test despite the presence of a radiologically evident residual mass. PET and CT were disconcordant in 37.4% and 23% in group 2 and 3 patients respectively, but only 11.3% of the patient did a biopsy. In the current study, biopsy was positive only patients were both tools were positive. In our study, PET has a statistically significant higher sensitivity, specificity, and more importantly, nearly no false negative results.

PPV for PET was 40.7%, compared to 14.5% for CT scan ($p < 0.001$), indicating a considerable number of false positive results when using conventional CT. This could be explained by the presence of non viable fibrotic residue falsely taken as a positive test. We could depend with confidence on PET in confirming true negative results.

CT scan has a relatively high sensitivity and specificity for pretreatment staging of lymphoma. The high frequency of residual masses present in cases with initially bulky disease affects its specificity for post-treatment evaluation [32–35]. PET CT is not recommended in routine follow up after complete remission. It has a low PPV due to post therapeutic inflammation taken denoting high false positivity rather than true relapse [4]. Our study weakness is being a retrospective one, were different radiological assessment, and at different stages of disease. Further data on the significance of a PET CT at presentation, and time of evaluation in children with NHL is needed to better assess its role as a reliable tool for evaluation of response.

Conclusion and recommendations

PET scan is significantly more sensitive than conventional CT in the management of aggressive pediatric mature B cell NHL. It remains a good negative test. Further prospective study is needed to assess the reliability of such a tool in mature B cell lymphoma subtypes.

Conflict of interest

None declared.

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